PATENT
Customer No. 22,852
Attorney Docket No. 2405.0190-00

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Joost VAN NEERVEN	)	Group Art Unit: 1641
	)	
Serial No.: 09/467,901	)	Examiner: Pensee T. Do
	)	
Filed: December 21, 1999	)	Confirmation No.: 2936
	)	
For: A METHOD OF DETECTING AND/OR QUANTIFYING A SPECIFIC IGE ANTIBODY IN A LIQUID SAMPLE	)	

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

In support of the Notice of Appeal and Pre-appeal Brief Request for Review filed on October 6, 2005, Appellant presents this brief and encloses herewith a check including the fee of $500.00 required under 37 C.F.R. § 41.20(b)(2). Appellant files this Appeal Brief with a Request for Oral Hearing, a Petition for an Extension of Time for 3 months, and the appropriate fees.

This Appeal responds to the final rejection of claims 1-6 and 8-23.

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Real Party in Interest

ALK-ABELLÓ A/S is the real party in interest by virtue of an assignment recorded on April 10, 2000, at Reel 010735, Frame 0631.

Related Appeals and Interferences

There are currently no other appeals or interferences, of which Appellant, Appellant's legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of the Claims

Of the 22 claims in the original application, claim 7 was canceled in the Amendment of September 26, 2003. Appellant added claim 23 in the Amendment of January 7, 2005. Thus, the claims on appeal are claims 1-6 and 8-23. Appellant notes that claim 15 is currently neither objected to or rejected and therefore presumably

allowable. But in the Advisory Action dated September 8, 2005, the Examiner included claim 15 without basis, in the list of claims under rejection. See page 1 of the Advisory Action dated September 8, 2005. Thus, while disagreeing with the status of claim 15, Appellant includes it in Appendix 1, which provides a listing of the claims on appeal.

Status of Amendments

Appellant filed an Amendment After Final on July 6, 2005. According to the Advisory Action dated September 8, 2005, the Examiner entered this amendment into the record.

Summary of the Claimed Subject Matter

The claims of the invention on appeal relate to methods of detecting or quantifying IgE antibodies in a way that accounts for the normal antibody *in vivo* interactions within a person. See specification at page 3, lines 22-26. To facilitate the Board's appreciation of these *in vivo* antibody interactions, Appellant provides a brief background on the structure and function of antibodies. In general, antibodies are an important component of the immune system because of their ability to effect the control of infection and eradicate the pathogens that cause them. These "effector" functions include, for example, complement activation, opsonization of pathogens, agglutination, neutralization of pathogens, mast cell sensitization, and eosinophil activation. From this list, you will see below that mast cell sensitization and eosinophil activation are particularly relevant to IgE antibodies. *Id.*

Structurally, antibody molecules are "Y" shaped. *Id.* at page 1:19. Each of the two upper prongs of the "Y" contain a variable region that binds to a specific molecule called a ligand. Ligands include antigens, other antibodies, or haptens. Thus, each

antibody binds to two target molecules and this variable region confers specificity to the antibody. The bottom stem of the "Y" represents the constant region, which is used to define the class of the antibody. The constant region mediates the antibody effector functions referred to above. There are 5 known classes of antibodies: IgA, IgD, IgE, IgG, and IgM. IgE antibodies are particularly important because their effector functions act on cells, especially mast cells, that participate in allergic reactions. Mast cell activation triggers an immediate allergic reaction in a person, leading to a variety of conditions including edema, vasodilation, tracheal occlusion, bronchial constriction, and death, depending on the allergen and the severity of the reaction. T cells, which will be discussed later, participate in a later stage of an allergic response.

As suggested above, an IgE antibody performs its effector functions by binding to two IgE receptors located on a variety of cells. As the specification explains, and getting to the specific issue here, eosinophils, activated B lymphocytes, activated T lymphocytes, and dendritic cells express the first receptor, the low-affinity IgE receptor, CD23 or FcεRII. See page 4, lines 16-18. CD23 primarily binds to complexes containing multiple IgE molecules bound to antigens. *Id.* at lines 20-23. Mast cells, basophils, Langerhans cells, monocytes, and dendritic cells express the second IgE receptor, FcεRI. *Id.* at lines 30-33. Like CD23, the high-affinity FcεRI receptor has also been shown to bind complexes containing multiple IgE antibody molecules. See specification at page 4, line 34 to page 5, line 2.

Thus, when considering the *in vivo* interactions of an antibody, there are three major components: (1) the IgE antibody itself; (2) the ligand; and (3) the IgE receptor. The claimed methods mimic the *in vivo* interactions between these components to

provide not just a measurement of all IgE in a sample, but rather a more complete measurement of those IgE antibodies capable of exerting their effector functions. In other words, the claimed invention identifies those IgE antibodies that are physiologically active. See specification at page 3, lines 27-30; page 6, lines 1-16. Several features of the claims on appeal achieve this goal. Appellant will discuss claim 1 as an example. These features are shared throughout the independent claims on appeal. All of these features coordinate to produce a method of detection that parallels as closely as possible the interactions of the ligand, the IgE antibody, and the receptor. First, the invention uses a liquid sample, which can be any liquid or liquified sample. See specification at page 14, lines 24-29. By using a liquid sample, the invention provides an environment in which reactants are free to interact with each other as they would in a fluid *in vivo* environment. See specification at page 3, lines 24-26.

Second, the invention uses a free dissolved ligand. As the specification explains, a free ligand is unhindered to form complexes with IgE antibodies. See page 15, lines 30-31. These ligands can be in solution or coupled to a substance in suspension. *Id.* at lines 31-35. By not tethering the ligand to an immobilized surface, the ligand is free to interact with IgE antibodies in a way similar to *in vivo* interactions.

Third, the invention uses IgE receptors bound to a carrier. This aspect of the invention provides two important features that serve to mimic *in vivo* interactions. IgE antibodies exert their biological function by binding to IgE receptors. Prior systems that use, for example, anti-IgE antibodies to bind to the IgE antibodies are artificial and useful for simply measuring the concentration of specific immunoglobulins in a sample. In fact, it can be said that prior systems are artificial because they measure the total

concentration of immunoglobulin in a sample. See specification at page 1, lines 9-29. In contrast, however, by using IgE receptors, the invention focuses on those antibodies that are biologically active, thus measuring the relevant *in vivo* level of IgE. See specification at page 6, lines 1-6.

Furthermore, to accommodate for the fact that different IgE receptors are expressed on different cell populations and have different impacts on the immune status of a patient, the invention allows for the use of these receptors separately or together. This provides a detailed picture of the immunological status of a patient with regard to a particular allergen. See specification at page 6, lines 6-16; page 6, line 34 to page 7, line 2; page 11, lines 5-8 and lines 27-31. The second component of the invention that distinguishes it from more artificial tests is that the receptor is bound to a carrier. It must be remembered that *in vivo*, receptors are expressed on cells. Thus, attaching the receptor to a carrier mimics receptor expression on a cell. In fact, the specification also contemplates using cells as carriers. See page 13, line 9.

Finally, the order in which the IgE antibody, ligand, and receptor interact with each other *in vivo* is an important aspect of the invention. The free ligand and IgE antibodies in the sample interact with each other before exposure to an IgE receptor or at the latest, simultaneously with exposure to the receptor. See specification at page 5, lines 7-20; page 10, lines 4-13. In the human system, free ligand and antibody too would interact prior to or at the same time as interaction with the receptor.

Moreover, by using a free ligand and a carrier bound receptor in a liquid sample, ligands and receptors are also free to interact with potentially interfering substances in the sample such as other immunoglobulins. See specification at page 5, lines 22-33.

Thus, rather than optimizing the detecting of all IgE specific for a particular ligand in the sample, the invention focuses on those IgE antibodies that are most likely to be active *in vivo* by virtue of binding to ligand and to an IgE receptor despite potential interference components in the sample environment.

The distinction between measuring total IgE antibodies specific for a given allergen and measuring physiologically active IgE antibodies is an important one to make in the context of patients suffering from allergies. For example, people with severe allergies can receive treatment that eventually desensitizes them to an allergen. In a treatment called Specific Allergy Vaccination (SAV), patients receive low doses of allergen over a long period of time. After SAV treatment, the level of allergen-specific IgE antibodies remains the same and yet the patient's sensitivity to the allergen decreases. This is unusual, because as discussed above, IgE antibodies mediate allergic reactions. Two mechanisms have been suggested to explain this. As the specification explains, SAV treatment results in an inhibition or reduction of IgE binding to its receptors. See page 6, lines 21-23. Thus, even though the amount of allergen-specific IgE remains unchanged, the percentage of physiologically active IgE decreases. Significantly, since the conventional method simply detects all allergen-specific IgE antibodies, it would not register this distinction. The results of the method of the invention, however, would reflect the true status of the patient. See specification at page 6, lines 22-32; Example 2; Amendment dated January 7, 2005 at page 14. In other words, the results would show a decreased concentration of physiologically active IgE, which would correspond to the patient's loss of sensitivity to the allergen.

The method of the invention would also take into consideration the second proposed mechanism behind the success of SAV treatment. B cells, macrophage, monocytes, and dendritic cells, all of which express IgE receptors, can present allergens to T cells. Normally, the allergen binds to IgE antibodies which in turn bind to the receptors on these antigen presenting cells (APCs). These APCs then interact with T cells causing a change in the profile of cytokines that are produced in the immune response. Researchers have shown that the interaction of IgE with its receptor is critical to the process of antigen presentation in this context. The change in the profile of cytokines produced by T cells leads to the production of IgG antibodies that are also specific for this allergen. These IgG antibodies compete with IgE antibodies for binding to circulating allergen. Thus, these IgG antibodies interfere with IgE binding to the allergen and subsequent binding to the IgE receptors. As discussed above, the method of the invention allows for the interaction of such interfering components in the sample.

Grounds of Rejection

Claims 1-5, 8-14, 16, and 21-23 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Pat. 6,087,188 (Johansen) in view of U.S. Patent 6,034,066 (Johnson) and U.S. Patent 6,060,326 (Frank 2).[1, 2]

Claims 6 and 17-20 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Johansen and in further view of Frank 2 and U.S. Patent 6,004,745 (Arnold).

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[1] Appellant discusses only one reference by Frank in this brief. To keep the reference nomenclature in this brief consistent with the prosecution history, however, Appellant has designated the '326 patent as "Frank 2."

[2] As Appellant noted, claim 15 is listed as rejected on page 1 of the last Advisory Action. This is clearly a clerical error based on the status of this claim in the prosecution history. See for example, Office Action dated December 16, 2003 at page 2.

Arguments

I. Claims 1-5, 8-14, 16, and 21-23 are not obvious in view of Johansen, Johnson, and Frank 2.

A. Claims 1, 8-14, and 16

- Johansen

Examiner Do (the Examiner) contends that Johansen teaches roughly three things. First, it allegedly teaches a method of detecting an antibody using a labeling compound and comprising the steps of mixing the ligand bound to biotin with the sample. Office Action dated March 1, 2001 at page 6.[3] Second, it allegedly discloses the use of an antibody directed against the antibody to be detected bound to paramagnetic particles and a chemiluminescent compound bound to avidin. The method then allegedly separates the solid phase from the liquid phase before analyzing the solid phase for the presence of a chemiluminescent complex. *Id.* at pages 6 and 7. Third, according to the Examiner, Johansen also teaches a "parallel reference immunoassay" in which the light emission of a complex comprising a captured specific antibody coupled to a chemiluminescent label is compared to the light emission in a parallel assay for the class of antibodies. *Id.* at page 7.

The Examiner acknowledges, however, that Johansen does not teach using an IgE receptor to detect or quantify IgE. Office Action dated March 26, 2003 at page 9. The Examiner further states that this reference does not teach a method of IgE detection using CD23 alone to make a first measurement followed by using the Fcεl receptor alone to make a second measurement. *Id.*

[3] The Examiner's description of these references remained constant throughout the prosecution history of this application. In each subsequent Office Action, the Examiner restated the alleged teachings of each reference and then added a new section to address Applicant's arguments.

- Johnson

Regarding Johnson, the Examiner alleges that this reference teaches the role of CD23 in regulating the immune response, particularly IgE responses. *Id.*

- Frank 2

The Examiner believes that Frank 2 teaches a method for detecting IgE antibodies using a human Fc epsilon receptor. *Id.*

- Combination

The Examiner combines Johansen, Johnson, and Frank 2, suggesting that it would have been obvious to one of ordinary skill in the art to use the IgE receptors allegedly taught in Johnson and Frank 2 to measure IgE according to the method of Johansen. *Id.* at page 10. In addition, with regard to claim 16, which describes the ratio of ligand to IgE to be detected, the Office believes it would have been obvious to use enough ligand molecules to optimize binding of all the IgE molecules in a sample.

- *In vivo* Conditions

Independent claim 1 has the key features discussed in the Summary section above. Appellant will discuss these claims in regard to those features and the references cited by the Examiner. The method of the invention invokes a combination of features that result in mimicking the interactions antibodies have *in vivo* with their associated ligands and receptors. With this in mind, the Examiner credits the assay in Johansen as using an anti-IgE antibody rather than an IgE receptor. As a result, Johansen's assay is similar to a conventional assay discussed in the Summary section in that it is designed to simply detect all IgE antibody specific to a particular ligand in a sample. In short, Johansen does not teach the use of an IgE receptor or provide the

motivation to make the substitution the Examiner suggests. *Id.* at page 18. Likewise, Johnson's general teaching on the role of CD23 in the immune response does not salvage Johansen and does not invoke the specific concept of a method of detecting IgE antibodies using IgE receptors. *Id.* Finally, Frank 2 does not motivate the skilled artisan to use a free dissolved ligand and a carrier-bound IgE receptor. *Id.* Thus, there is no guidance in these references that would allow the skilled artisan to arrive at the unique combination of features the invention provides to mimic *in vivo* interactions. See Amendment dated June 16, 2004 at pages 16 and 17.

In an Office Action dated September 8, 2004, the Examiner responded to this argument by contending that the features of the invention discussed by Appellant, i.e., simulating interference from other components in the sample and mimicking *in vivo* interactions, were not recited in the rejected claims. See page 7. These aspects of the invention are implicit in the independent claims because of their features as discussed in the Summary section above. Thus, Appellant did not believe that amendment of these claims was necessary. But in an effort to work within the Examiner's position, Appellant requested an interview to discuss potential alternate claim formats. It is worth noting that the Primary Examiner, Christopher L. Chin, who signed the majority of Office Actions in the prosecution history of this application, was not present at the interview, contrary to what was expected. Appellant's representatives were not notified of his absence until arriving for the interview. During this interview of November 19, 2004, however, Appellant's representatives provided possible alternative claims to the Examiner who, because of her junior status, was not able to make any decisions on those claims to advance prosecution. Instead, Examiner Do invited an officemate,

Examiner Long Le, who had limited interaction with the application, to look at the claims.[4] Based on this interview, Appellant introduced claim 23, discussed below, to make explicit what was already implicit in the claims.

- Motivation to Combine

There are several reasons why the Examiner has failed to show a motivation to combine these references. For her primary argument, the Examiner has suggested that the skilled artisan would use the FcεRI and CD23 (FcεRII) receptors in Johansen's method because (a) both receptors are specific to IgE and (b) because these receptors allegedly demonstrate less cross-reactivity and more sensitivity than anti-IgE antibodies, citing Frank 2 at col. 1, lines 19-34. See Office Action dated December 16, 2003 at pages 5 and 6. This is not correct. First, Frank 2 discusses only the high-affinity receptor, FcεRI. Thus, by including CD23 in the alleged teaching of Frank 2, the Examiner reads into this reference a teaching that is not there. Second, as Appellant noted, Frank 2 discusses canine IgE receptor, not human IgE receptors. See Amendment dated July 6, 2005 at page 18. Frank 2 does not suggest that the CD23 IgE receptor shares these characteristics of greater specificity and reduced cross-reaction. As discussed in the Summary section above, such rationale is reflective of the desire to maximize the detection of all IgE in a sample. This goal is directly contrary to the invention's purpose of performing the method in such a way that the cross-reactions that would happen *in vivo* are reproduced. In other words, the present invention

[4] Appellant notes that Examiner Le signed the first Office Action dated March 1, 2001, which was over 3 years prior to the interview. Since then, Examiner Le signed the last Advisory Action and nothing more.

simulates interference from other components in the sample as well, and not simply maximum IgE detection. See Amendment dated June 16, 2004 at page 14.[5]

It is worth noting that, even if the Examiner's citation to Frank 2 provided a motivation to use an IgE receptor, which Appellant does not believe it does, then the skilled artisan would be encouraged to use Frank 2's method *in its entirety*. See Amendment dated June 16, 2004 at pages 16 and 17. And, *arguendo*, if Frank 2 teaches away from using anti-IgE antibodies as a capture reagent by suggesting the use of an IgE receptor, why would the skilled artisan combine this reference with Johansen, a reference that uses a anti-IgE antibodies as capture reagents and does not even discuss using IgE receptors?

In addition, the Examiner incorrectly asserts that Johansen teaches using the reagents of Frank 2 in its method steps. Office Action dated September 8, 2004 at page 9. But, as the Appellant noted previously, Frank 2 describes using FcεR with antibodies, not substituting antibodies for receptors. Frank 2 makes this clear when it states "the present invention can include not only a FcεR but also one or more additional antigens or antibodies useful in detecting IgE. . . Examples of antibodies used in the present invention include antibodies that bind selectively to the constant region of an IgE [antibody]." Conversely, Johansen's method uses only anti-IgE antibodies.

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[5] In this Amendment which was filed with an RCE, Applicant requested an interview with the Examiner and on August 20, 2004, left a voice mail with the Examiner reiterating this request for an interview. On August 25, 2004, the Examiner contacted Applicant's representative indicating that she needed to act on the application quickly and would grant an interview in two days. Unfortunately, such short notice did not make an interview possible at that point in prosecution. An interview was eventually conducted on November 19, 2004.

Thus, the two references necessarily disclosed different reagents. See Amendment dated January 7, 2005 at page 15.

Moreover, the Examiner also stated that if Frank 2 and Johansen used the same methods and same reagents, they would have been cited in an anticipation rejection, not an obviousness rejection. Office Action dated September 8, 2004 at page 9. Given this statement, the Examiner's use of these references in an obviousness rejection suggests that the Examiner realizes that Frank 2 and Johansen do not disclose the same methods and reagents. Appellant finds this confusing, as the logical conclusion based on the Examiner's statement directly contradicts the Examiner's prior description of these references as discussed above.

In attempting to address the above points, the Examiner responded by expanding the citation to Frank 2 to include col. 2, lines 13-17 and col. 8, lines 50-56. See Office Action dated April 6, 2005 at pages 8 and 9. Neither citation, however, can cure the lack of motivation to combine Johansen, Johnson, and Frank 2. The first citation, which states that "the invention [of Frank 2] relates to the discovery that purified, high affinity canine Fc epsilon receptor . . . can be used in canine epsilon immunoglobulin (referred to herein as IgE or IgE antibody)- based detection . . . methods and kits," appeared to suggest that FcεR could be used in canine IgE based detection methods. See Amendment dated July 6, 2005 at page 18. But a general suggestion that an IgE receptor might be used in the genus of detection assays does not suggest its use in the particular method of the invention. *Id.* Again, there is no guidance in these references that instructs the artisan as to what aspects of each reference should be chosen to arrive at the invention. The second citation to Frank 2,

which suggests that "a complex can be detected in a variety of ways, including . . . a particulate-based assay (e.g., using particulates such as . . . magnetic particles . . .)," allegedly teaches that a complex can be detected in particulate-based assays. But this citation does not explain in what capacity the particulates would be used, (i.e., if the particulate would be attached to the receptor or the ligand). See *id.* The general teaching of a component in a reference does *not* necessarily mean that the component will be used in the same way in the reference as in the invention. See *id.*

In her last attempt to find support from Frank 2, the Examiner cited to two additional passages from Frank 2. See Advisory Action dated September 8, 2005 at page 8. The first teaches in part that "a complex can be formed in which one or more members of the complex are immobilized on (e.g., coated onto) a substrate. . . Suitable substrate materials include . . . . particulate materials such as latex, polystyrene, nylon, nitrocellulose, agarose, and magnetic resin." The second teaches that a preferred immunosorbent assay includes the step of binding a canine FcεR to a substrate prior to contacting the FcεR molecule with a putative IgE-containing composition. *Id.* Appellant notes that also provided in this list are substrates that do not float freely in solution such as a microtiter dish, a plate, a dipstick, a membrane, a filter, a tube, and a dish. Once again, neither passage helps the Examiner's motivation to combine argument.

Given the list of substrates provided in Frank 2, this second citation could refer to coating a microtiter plate with canine FcεR as easily as it might refer to coating a particle. Thus, we are left with the fact that the Examiner has still not explained why out of this list, the artisan would be motivated to choose a particulate. If anything, when describing other embodiments, this reference more consistently discusses non-soluble

substrates, such as a microtiter dish or a dipstick. See, e.g, col. 11, lines 28-30 and 54-56; col. 12, lines 27- 32; col. 13, lines 26-30.

- Expectation of Success

The Examiner did not provide a basis for showing a reasonable expectation of success in combining the references. Not only was there no motivation to combine Johansen, Johnson, and Frank 2, the Examiner did not point to evidence to show that the skilled artisan would have a reasonable expectation of success in using IgE receptors in Johansen's assay. See Amendment dated January 7, 2005 at page 16. In the last Advisory Action, the Examiner asserted that such a basis had been provided. The basis, however, was founded in an alleged motivation to combine. See Advisory Action dated September 8, 2005 at pages 9 and 10. With all due respect to the Examiner, Appellant believes the Examiner has confused the required elements of motivation to combine and reasonable expectation of success. Moreover, the Examiner improperly tries to shift the initial burden of showing an expectation of success to Appellant by suggesting that Appellant did not point to any factors that would prevent a skilled artisan from having a reasonable expectation of success in combining the references. *Id.* at page 10. Demonstrating a reasonable expectation of success is part of the Examiner's initial burden of presenting a *prima facie* case of obviousness. See *In re Kumar*, 418 F.3d 1361, 1366 (Fed. Cir. 2005) (citing *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992)); M.P.E.P. § 2142 (October 2005).

B. Claim 2

Independent claim 2 also has the key features discussed in the Summary section above. Because these features are also present in claim 1, Appellant's arguments with

respect to the non-obviousness of claim 1 also apply to claim 2. Unlike claim 1, claim 2 specifies that the ligand is labeled.

C. Claims 3, 8, and 9

Independent claim 3 also has the key features discussed in the Summary section above. Because these features are also present in claim 1, Appellant's arguments with respect to the non-obviousness of claim 1 also apply to claim 3. Unlike claim 1, claim 3 specifies that the ligand is bound to a label compound.

D. Claims 4, 8, and 9

Independent claim 4 also has the key features discussed in the Summary section above. Because these features are also present in claim 1, Appellant's arguments with respect to the non-obviousness of claim 1 also apply to claim 4. Unlike claim 1, claim 4 specifies that the sample, the free dissolved ligand and a label compound are brought together.

E. Claims 5, 8, and 9

Independent claim 5 also has the key features discussed in the Summary section above. Because these features are also present in claim 1, Appellant's arguments with respect to the non-obviousness of claim 1 also apply to claim 5. Unlike claim 1, claim 5 specifies contacting the sample with the free dissolved ligand to form a mixture I, mixing the carrier-bound receptor with mixture I, and then adding a label compound.

G. Claim 21

Independent claim 21 also has the key features discussed in the Summary section above, those being a liquid sample, a free ligand, a carrier-bound IgE receptor, and exposing the ligand to the sample before adding the receptor. Because these

features are also present in claim 1, Appellant's arguments with respect to the non-obviousness of claim 1 also apply to claim 21. Unlike claim 1, claim 21 provides a method for monitoring and evaluating the immunological status of a subject which includes obtaining a liquid sample suspected to contain IgE from the subject in addition to the method steps of claim 1.

H. Claim 22

Independent claim 22 also has the key features discussed in the Summary section above. Because these features are also present in claim 1, Appellant's arguments with respect to the non-obviousness of claim 1 also apply to claim 22. Unlike claim 1, claim 22 provides a method of monitoring and evaluating the immunological status of a subject receiving SAV treatment which includes obtaining a liquid sample suspected to contain IgE from the subject in addition to the method steps of claim 1.

I. Claim 23

Independent claim 23 also has the key features discussed in the Summary section above. Because these features are also present in claim 1, Appellant's arguments with respect to the non-obviousness of claim 1 also apply to claim 23. Claim 23 provides an explicit description of which *in vivo* interactions are simulated in the claimed method, an explicit description of the order in which the antibody, ligand, and receptor contact each other, and recites that physiologically active forms of IgE are measured.

Based on the interview of November 19, 2004, discussed above, Appellant introduced claim 23 to make explicit what was already implicit in the claims. In the

subsequent Office Action, the Examiner did not give patentable weight to the term "simulating *in vivo* interactions" as recited in claim 23's preamble because the Examiner believed this phrase was indefinite. See Office Action dated April 6, 2005 at page 6. Appellant explained that the conditions being simulated were the *in vivo* interactions between the IgE antibody, the ligand, and the receptor as recited in the preamble. See Amendment dated July 6, 2005 at pages 13 and 14. The Examiner then withdrew this indefiniteness rejection. See Office Action dated September 8, 2005 at page 2. Thus, the Examiner treated claim 23 identically to the other rejected claims. However, in this Office Action, the Examiner admitted that Johansen did not teach an assay simulating *in vivo* interactions between the ligand, the IgE antibody, and the IgE receptor. *Id.* at page 5.

Based on a teleconference with the Examiner on June 21, 2005, Appellant amended claim 23 to move simulating *in vivo* interactions from the preamble into the body of the claim. See Amendment dated July 6, 2005 at page 16. Regarding claim 23, in the Advisory Action dated September 8, 2005, the Examiner contends that the combination of Johansen, Frank 2, Johnson, and Arnold[6] teach that the IgE and the ligand bind to each other before contact with an IgE receptor. See page 12. The Examiner reasoned that this alleged teaching satisfied simulating *in vivo* interactions between the IgE antibody, the ligand and the receptor because step b of claim 23 that to mimic *in vivo* interactions the ligand should bind to the IgE antibody before binding to the receptor. *Id.* As Appellant has explained throughout prosecution, though, the simulation of *in vivo* interactions happens because of several features mentioned in the

[6] Arnold is discussed below in the context of the second rejection on appeal.

claim. The order of the interaction between the IgE antibody, the ligand, and the receptor is just one of them. Arguendo, even if the Examiner were correct in her assessment of the teaching of these references, this single teaching would not cause the artisan to arrive at the combination of all the elements recited in, for example, claim 23 that lead to the simulation of IgE antibody *in vivo* interactions.

Moreover, Appellant respectfully disagrees with the Examiner's summary of these references with respect to this issue. Neither Johansen, Johnson, nor Arnold provide any teaching on IgE receptors let alone in what order an IgE antibody, its ligand, and the receptor should complex with each other. Regarding Frank 2, as Appellant explained, this reference either omits the step of mixing the ligand with IgE in a sample or adds the ligand after IgE has bound to the IgE receptor. See Amendment dated June 16, 2004 at page 16. Thus, the combination of these references does not give rise to step b as recited in claim 23.

- Conclusion

In sum, the prosecution history of this rejection clearly shows that claims 1-5, 8-14, 16, and 21-23 are not obvious in view of Johansen, Johnson, and Frank 2. The Examiner has admitted that Johansen does not teach an assay that mimics *in vivo* interactions between an IgE antibody, its ligand, and its receptor. Neither Frank 2 nor Johnson remedy this defect in Johansen. The rejected claims either implicitly or expressly convey this concept. The Examiner's citations to Frank 2 do not provide a motivation to combine the references as the Examiner suggests. And the Examiner did not provide any basis for believing that there would be a reasonable expectation of success in combining the references.

II. Claims 6 and 17-20 are not obvious in view of Johansen, Frank 2 and Arnold.

A. Claim 6[7]

When rejecting claims 6 and 17-20, the Examiner applied Johansen and Frank 2 as discussed above. These references, the Examiner admits, do not teach adding a label after a first separation step followed by a second separation step to separate non-complexed labels. See Office Action dated March 26, 2003 at page 11. The Examiner invokes Arnold for the alleged discussion of a sandwich assay combining an immobilized antibody[8] with a test medium so that antigens will bind to the immobilized antibody. Unbound antigen is allegedly removed in a first separation step after which a labeled antibody is added, thus sandwiching the antigen between the immobilized antibody and the labeled antibody. A second separation step then presumably removes any unbound labeled antibody. The Examiner combined these references, suggesting that it would have been obvious to add a label molecule after a first separation step and then separate the non-complexed labels in a second separation step using the reagents in Johansen's method as modified by Frank 2. *Id.* at page 12. The Examiner acknowledges that separation steps are time consuming, but believes that they increase assay sensitivity and eliminate cross-reaction between the label and the immobilized antibody. *Id.*

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[7] The Examiner did not include claims 8 and 9, which also ultimately depend on claim 6, in this rejection. Since claims 8 and 9 are not subject to rejection in light of Johansen, Frank 2, and Arnold, Appellant concludes that claims 8 and 9 are allowable with respect to claim 6.

[8] When describing Arnold, the Examiner provides a parenthetical description of the immobilized reagent as an IgE receptor. The citation given by the Examiner, however, does not recite an IgE receptor, it merely discusses an immobilized antibody. Indeed, Arnold does not discuss an IgE receptor at all.

Independent claim 6 recites two separation steps. More importantly, it also shares the features of the invention that lead to simulating the *in vivo* interactions of IgE antibodies: a liquid sample, a free dissolved ligand, an IgE receptor bound to a carrier, and exposure of the ligand to the antibody before exposure to the receptor. As discussed above, the combination of Johansen and Frank 2 provide neither the requisite motivation to combine these references nor a reasonable expectation of success in doing so. Arnold's discussion of a sandwich assay in the background section of this patent does not cure these defects either. This sandwich assay detects the presence of a ligand, not the presence of a physiologically active antibody specific for a ligand. Arnold considers antibodies more so as reagents for detecting a ligand. See col. 6, lines 58-59. Moreover, Arnold teaches immobilization of a capture antibody, thus the interaction between the antibody and the ligand does *not* take place freely in solution. In contrast, as noted above, the ligand of the invention is a free, dissolved ligand that can interact freely with IgE antibodies in the liquid sample. See Amendment dated September 26, 2003 at page 19. There is no teaching in Arnold suggesting that such an assay could be adapted to detect antibodies let alone using an antibody receptor that is not immobilized to do it.

If anything, Arnold teaches away from heterogenous assays that use two separation steps. The thrust of Arnold's invention is to develop a method that increases sensitivity over heterogenous assays by avoiding separation steps. *Id.* Such homogenous assays use a label that undergoes a detectable change once the ligand to be detected binds. *Id.* Thus, Arnold does not encourage the use of one separation step, let alone two. When considering the teachings of Arnold in the context of

Johansen and Frank 2, the combination of these three references cannot obviate the rejected claims.

In addressing this issue, the Examiner responded by citing to col. 2, lines 16-20 of Arnold. That section allegedly explains that the invention of Arnold also provides methods for increasing the sensitivity of assays which involve separation by combining the homogenous method of Arnold's invention with other separation methods to reduce non-specific background. See Office Action dated December 16, 2003 at page 9. Thus, the Examiner concludes, Arnold's invention includes a heterogenous assay with a separation step. *Id.* The Examiner's summary of Arnold is not accurate though. Arnold's methods use a label that undergoes a change in stability once a ligand binds. See Arnold, col. 5, lines 7-19. Typical heterogenous assays use labels that do not change in the presence of a ligand. *Id.* While Arnold may discuss the use of an optional separation step, it is in the context of decreasing background noise in homogenous assay formats. *Id.* Thus, Arnold's disclosure focuses on homogenous assay formats using special labels. The Examiner acknowledged one of several negative impacts a separation step can have on an assay, increasing the amount of time it takes to perform the assay. See Office Action dated March 26, 2003 at page 12. Arnold cites this caveat and more as a basis for developing homogenous assays that do no require separation steps as conventional heterologous assays do. See Arnold at col. 5, lines 10-20.

Moreover, whether or not Arnold teaches heterogenous assays is really not relevant since the reference itself cannot remedy the lack of motivation to combine this reference with Johansen and Frank 2. Nor does it remedy the lack of a reasonable

expectation of success in combining the references. The Examiner did not explain why the skilled artisan would replace only the immobilized antibody with an IgE receptor, instead of replacing both the immobilized and the labeled antibody with an IgE receptor. See, e.g., Amendment dated June 16, 2004 at pages 20 and 21; Amendment dated January 7, 2005 at page 18; Amendment dated July 6, 2005 at page 20.

In the Office Actions that followed, the Examiner consistently responded by suggesting that the combination of Johansen and Frank 2 alone provided the required elements of motivation to combine and reasonable expectation of success. See, e.g., Office Action dated September 8, 2004 at page 10; Office Action dated April 6, 2005 at pages 10 and 11. Thus, according to the Examiner, the teaching of Arnold need not cure those deficiencies. The Examiner relied upon Arnold for teaching separation steps, which as Appellant has explained is not the thrust of Arnold. See Office Action dated April 6, 2005 at page 11. The Examiner's explanation that the skilled artisan would be motivated to use such separation steps does not address the motivation to combine Arnold with the teachings of Johansen and Frank 2. *Id.*

In the last Advisory Action, the Examiner provided a more detailed explanation of how she believed Arnold applied to Johansen and Frank 2. In the method of Johansen and Frank 2, the Examiner explained, IgE is being detected and the label must have some means for binding to the IgE. See Office Action dated September 8, 2005 at page 11. According to the Examiner, such means could come in the form of an antibody or a receptor and either one would allegedly serve the same purpose. *Id.* Thus, the Examiner concludes, the skilled artisan would be able to figure out which reagent to use and have a reasonable expectation of success in doing so. *Id.* The Examiner believes,

apparently, that the issue of knowing which of Arnold's antibodies to substitute is not important because she relies on Arnold for allegedly teaching a separation step. *Id.*

Appellant finds several flaws associated with the Examiner's reasoning. First, *arguendo*, if as the Examiner suggests, antibodies and receptors would work equally well in Arnold's assay then there is no motivation to make the specific substitution of a receptor for the immobilized antibody while not substituting the labeled antibody. Appellant respectfully disagrees with the Examiner that this point is not important. The motivation to combine speaks to the motivation to combine all three references cited against the claims. Whether or not Arnold is simply cited for teaching a separation step, there still must be some nexus that suggests a combination that results in the claimed invention. See *Medichem, S.A. v. Rolabo, S.L.*, 2006 U.S. App. LEXIS 2653, at *14-15 (Fed. Cir. Feb. 3, 2006); M.P.E.P. § 2142 (October 2005). Finally, the Examiner's assertions that the skilled artisan would know which reagent to use and have a reasonable expectation of success in doing so represent the Examiner's opinions and are not supported by factual evidence. Throughout the prosecution history of this rejection based on Johansen, Frank 2, and Arnold, the Examiner did not provide any other basis to support the reasonable expectation of success component of a *prima facie* case of obviousness.

B. Claims 17-19

Like claim 6, independent claim 17 also has the key features discussed in the Summary section above and recites two separation steps. Because of these commonalities between claim 6 and claim 17, Appellant's arguments with respect to the

non-obviousness of claim 6 also apply to claim 17. Unlike claim 6, claim 17 recites a label compound coupled to an antibody to the IgE to be detected.

C. Claim 20

Like claim 6, independent claim 20 also has the key features discussed in the Summary section above and recites two separation steps. Because of these commonalities between claim 6 and claim 20, Appellant's arguments with respect to the non-obviousness of claim 6 also apply to claim 17. Unlike claim 6, claim 20 recites method of detecting and/or quantifying a specific IgE antibody that uses a ligand bound to biotin and a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof, and involves initiating a chemiluminescent reaction followed by detecting or measuring the resulting chemiluminescence.

- Conclusion

In sum, as discussed in the rejection based on Johansen, Frank 2, and Johnson, the Examiner has not pointed to a motivation to combine these references or a reasonable expectation of success in doing so. In the present rejection, the removal of Johnson and the addition of Arnold does not cure these defects. Thus, the combination of Johansen, Frank 2, and Arnold cannot render claims 6 and 17-20 obvious.

Conclusions

For the reasons given above, pending claims 1-6 and 8-23 are allowable and Appellant requests reversal of the Examiner's rejection.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith,

including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 7, 2006

By: _____
Maryann T. Puglielli
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APPENDIX 1

Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes,

wherein the label to be detected is associated with the ligand or the IgE antibody and wherein the label to be detected is added to the complexes present in steps (a), (b), or (c) and does not form part of the carrier.

2. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved labeled ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

3. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten, wherein the ligand is bound to a label compound, to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

4. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten and with (iii) a label compound to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iv) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes,

wherein the label to be detected is associated with the ligand or the IgE antibody.

5. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) adding a label compound to the carrier-bound IgE-containing complexes formed in step (b),

(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes,

wherein the label to be detected is associated with the ligand or the IgE antibody.

6. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II,

(d) adding a label compound to the carrier-bound IgE-containing complexes resulting from the separation step (c) to form a mixture II',

(e) separating the labeled carrier-bound IgE-containing complexes from the mixture II', and

(f) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes,

wherein the label compound is associated with the ligand or the IgE antibody.

8. The method according to any one of claims 3-6, wherein the label compound is a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof and the ligand is bound to biotin or a functional derivative thereof.

9. The method according to claim 8, wherein the chemiluminescent compound is an acridinium compound.

10. The method according to claim 1, wherein the ligand is bound to biotin or a functional derivative thereof.

11. The method according to claim 1, wherein the IgE-containing sample is contacted with the ligand and allowed to incubate to form a mixture I (step (a)) before contacting mixture I with the carrier/IgE receptor (step (b)).

12. The method according to claim 1, wherein step (a) and (b) are carried out simultaneously in one operation.

13. The method according to claim 1, wherein the carrier is a particulate material.

14. The method according to claim 1, wherein the carrier is a paramagnetic particulate material.

15. The method according to claim 1, wherein the IgE to be detected is quantified using CD23 alone to obtain a first measurement and using FcεRI alone to obtain a second measurement, and using both the first and the second measurement as a basis for evaluating the immunological status of a subject.

16. The method according to claim 1, wherein the number of ligand molecules is between 100% and 200% of the number of IgE molecules to be detected.

17. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten, to form a mixture I comprising

complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II,

(d) adding a label compound coupled to an antibody to the IgE to be detected to the complexes present in steps (a), (b), or (c) above to form a mixture II',

(e) separating the labeled carrier-bound IgE-containing complexes from the mixture II', and

(f) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

18. The method according to claim 17, wherein the label compound is coupled to the antibody via biotin.

19. The method according to claim 17 or 18, wherein the label compound coupled to the antibody to the IgE to be detected is added to the carrier-bound complexes separated in step (c).

20. A method of detecting and/or quantifying a specific IgE antibody in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that

comprise the IgE antibody and the ligand (IgE-containing complexes), wherein the ligand is bound to biotin or a functional derivative thereof,

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(b') separating the carrier-bound IgE-containing complexes from the mixture II and washing said complexes,

(b") adding to the washed carrier-bound IgE-containing complexes a solution of (iv) a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof to form a mixture II',

(c) separating the carrier-bound IgE-containing complexes from the mixture II' and washing the complexes, and

(d) initiating a chemiluminescent reaction in the resulting IgE-containing complexes and detecting/measuring the resulting chemiluminescence, if any.

21. A method of monitoring and evaluating the immunological status of a subject comprising the steps of:

(a) obtaining a liquid sample suspected to contain an IgE antibody from the subject,

(b) contacting (i) the sample with (ii) a free ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(c) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes,

wherein the label to be detected is associated with the ligand or the IgE antibody and wherein the label to be detected is added to the complexes present in steps (b), (c), or (d) and does not form part of the carrier.

22. A method of monitoring and evaluating the immunological status of a subject receiving Specific Allergy Vaccination (SAV) treatment comprising the steps of:

(a) obtaining a liquid sample suspected to contain an IgE antibody from the subject,

(b) contacting (i) the sample with (ii) a free ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(c) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes,

wherein the label to be detected is associated with the ligand or the IgE antibody and wherein the label to be detected is added to the complexes present in steps (b), (c), or (d) and does not form part of the carrier.

23. A method of detecting and/or quantifying physiologically active forms of an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody by simulating *in vivo* interactions between the IgE antibody, the IgE antibody's ligand and the IgE antibody's receptor, comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes, and wherein the complexes that comprise the IgE antibody and the ligand are formed prior to contact with the IgE receptor to simulate *in vivo* interactions between the IgE antibody, the ligand, and the IgE receptor,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) detecting and/or quantifying physiologically active forms of ligand-specific IgE bound to said receptor by determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes,

wherein the label to be detected is associated with the ligand or the IgE antibody and wherein the label to be detected is added to the complexes present in steps (a), (b), or (c) and does not form part of the carrier and wherein *in vivo* interactions between the IgE antibody, the IgE antibody's ligand and the IgE antibody's receptor are simulated to measure physiologically active forms of IgE.

Appendix 2

Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

Appellant does not refer to any evidence in this Appeal Brief beyond evidence already of record, including Office Actions, responses to Office Actions, and references cited by the Examiner in the rejections on appeal.

Appendix 3

Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

There are currently no other appeals or interferences, of which Appellant, Appellant's legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.